(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 September 2005 (01.09.2005)

PCT

(10) International Publication Number
WO 2005/079880 A1

(51) International Patent Classification[7]: A61L 27/12, 27/56, A61F 2/28

(21) International Application Number: PCT/US2005/006100

(22) International Filing Date: 22 February 2005 (22.02.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/780,728 19 February 2004 (19.02.2004) US
10/852,167 25 May 2004 (25.05.2004) US

(71) Applicant *(for all designated States except US)*: CALCITEC, INC. [US/US]; 8201 Navidad Drive, Austin, Texas 78735 (US).

(72) Inventors; and

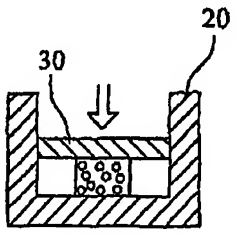
(75) Inventors/Applicants *(for US only)*: LIN, Jiin-Huey, Chern [US/US]; 911 Tower Road, Winnetka, Illinois 60093 (US). JU, Chien-Ping [US/US]; 16 Pinewood Drive, Carbondale, Illinois 62901 (US). TSAI, Chih-Hung; 3 Fl., No. 3-1, Lane 75, Taiping Road, Bei Chiu, Taichung (TW). TIEN, Yin-Chun; No. 40, Lane 93, Liming Road, Sanmin Chiu, Kaohsiung (TW). NING, Chao-Chin; 22, Jungshing Road, Yanchau Shiang, Kaohsiung (TW). CHAO, Chung-Po; No. 36-1, Yong-Fu E. St., Bade City, Taoyuan County (TW).

(74) Agent: MEYERTONS, HOOD, KIVLIN, KOWERT & GOETZEL, P.C.; Meyertons, Eric, B., P.O. Box 398, Austin, Texas 78767-0398 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,

[Continued on next page]

(54) Title: METHODS FOR PREPARING MEDICAL IMPLANTS FROM CALCIUM PHOSPHATE CEMENT AND MEDICAL IMPLANTS



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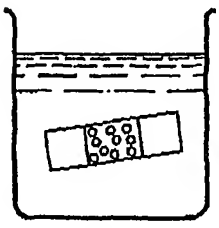

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(57) Abstract: The present invention discloses a medical implant made from calcium phosphate cement, and in particular to a method of preparing a molded and hardened calcium phosphate cement article having a superior compressive strength for use as medical implant. The molded and hardened calcium phosphate cement article may be in the forms of a dense block, a porous block for use as tissue-engineered scaffold, or a dual function block comprising a dense cortical portion bearing the majority of load and a porous cancellous portion allowing a rapid blood/body fluid penetration and tissue ingrowth.

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MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TITLE: METHODS FOR PREPARING MEDICAL IMPLANTS FROM CALCIUM PHOSPHATE CEMENT AND MEDICAL IMPLANTS

Field of the Invention

The present invention is related to a medical implant made from calcium phosphate cement, and in particular to a method of preparing a molded and hardened calcium phosphate cement article having a superior compressive strength for use as medical implant. The molded and hardened calcium phosphate cement block may be in the forms of a dense block, a porous block for use as tissue-engineered scaffold, or a dual function block comprising a dense cortical portion bearing the majority of load and a porous cancellous portion allowing a rapid blood/body fluid penetration and tissue ingrowth.

Background of the Invention

It is advantageous if a prosthetic bone implant is bioresorbable and is supportive at the same time. Accordingly, an article made of calcium phosphate will be preferable than that made of a metal, if the former has strength which is comparable to a human cortical bone. One way of making such a bone implant is by sintering a calcium phosphate powder, particularly a hydroxyapatite (HA) powder, into a block material at a temperature generally greater than 1000°C. Despite the fact that the high temperature-sintered HA block material has an enhanced strength, the bioresorbability of the material is largely sacrificed, if not totally destroyed, due to the elimination of the micro- and nano-sized porosity during the sintering process.

The conventional spinal fusing device is composed of a metallic cage and a bioresorbable material disposed in the metal cage, for example the one disclosed in US patent No. 5,645,598. An inevitable disadvantage of this fusion device is the sinking of the metallic cage sitting between two vertebrae to replace or repair a defect spinal disk, because the hardness and the relatively small size of the cage wear out or break the bone tissue, and in particular the endplate of the vertebra.

A tissue-engineered scaffold (majority made from biodegradable polymers) has a very porous structure that allows living cells (usually taken from the patient being treated) to penetrate into the structure and be "seeded" in-vitro during a cell culture process. After a period of time (days or weeks) of cell culture, the cell-seeded scaffold is implanted into either an animal (e.g., rat) whose immune system has been removed, or into the patient himself (usually under the skin for easier later-on process). During this period of time (weeks to months) the cells quickly multiply from absorbing nutrients from the animal or the patient's body, and, at the same time, the scaffold itself is gradually dissolved or resorbed. When this process is substantially "mature", the implant (now a real bone) is removed from under the skin of the animal or the patient and re-implanted into the (wounded or diseased) site being treated. The following are some references describing some details about the background, requirements, applications, etc. of tissue-engineered scaffold: US 6,139,578; US 6,200,606; US 5,306,303; and US 6,132,463.

It is advantageous if a tissue-engineered scaffold is bioresorbable, sufficiently porous and supportive at the same time. The conventional high temperature (usually >1000°C)-sintered porous hydroxyapatite (HA) block material does not possess sufficient micro/nano-sized porosity and is hardly bioresorbable. On the other hand, the conventional biodegradable polymer for scaffold application exhibits a relatively low strength and too high a dissolution rate.

Summary of the Invention

An objective of the invention is to provide a molded and hardened calcium phosphate cement (CPC) article or block having a superior compressive strength for use as medical implant, which is free from the aforesaid drawbacks in the prior art.

Another objective of the invention is to provide a porous hardened CPC article or block for use as a tissue-engineered scaffold, which is free from the aforesaid drawbacks in the prior art, or as a functional implant other than the tissue-engineered scaffold.

Another objective of the invention is to provide a dual function hardened calcium phosphate cement (CPC) article or block for use as a prosthetic bone implant comprising a dense cortical portion and a porous cancellous portion, which is free from the aforesaid drawbacks in the prior art.

The prosthetic bone implant constructed according to the present invention is made of a hardened calcium phosphate cement having an apatitic phase as a major phase, which comprises a dense cortical portion bearing the majority of load and a porous cancellous portion allowing a rapid blood/body fluid penetration and tissue ingrowth.

The prosthetic bone implant of the present invention is made by a novel technique, which involves immersing an article molded from two different pastes of calcium phosphate cement (CPC), one of them having an additional pore-forming powder, in a liquid for a period of time, so that the compressive strength of the molded CPC article is significantly improved after removing from the liquid while the pore-forming powder is dissolved in the liquid, creating pores in a desired zone or zones of the molded article.

Features and advantages of the present invention are as follows:

1. Easy process for different shape and size of the prosthetic bone implant of the present invention, so that the outer circumferential dense portion thereof can sit over the circumferential cortical portion of a bone and the porous portion thereof can contact the cancellous portion of the bone adjacent to a bone receiving treatment.

2. The dense cortical portion of the prosthetic bone implant made according to the present invention exhibits a high strength comparable to that of human cortical bone (about 110-170 MPa). The strength is adjustable by adjusting process parameters.

3. The dense cortical portion of the prosthetic bone implant made according to the present invention contains significant amount of micro- and nano-sized porosity, that improves bioresorbability thereof. Conventional high temperature-sintered HA block, on the other hand, does not possess sufficient micro/nano-sized porosity and is not bioresorbable.

4. The porous cancellous portion of the prosthetic bone implant made according to the present invention possesses a porosity greater than 40% in volume, prepferably 40-90%, allowing rapid blood/body fluid penetration and tissue ingrowth, thereby anchoring the prosthetic bone implant.

5. A wide range of medical application includes bone dowel, spacer, cavity filler, artificial disc and fixation devices for spine and other locations, to name a few.

In another aspect of the present invention, a novel method for making a hardened CPC article for use as medical implant is provided, which involves impregnating an article molded from a paste of CPC in a liquid for a period of time, so that the compressive strength of the CPC block is significantly improved after removing from the liquid. It is apparent that the medical implant prepared according to this novel method has the features and advantages recited in the above-mentioned Items 3 and 5.

In a further aspect of the present invention, a novel method for making a porous hardened CPC article for use as a tissue-engineered scaffold, which involves preparing a shaped article from a paste comprising a calcium

phosphate cement, a pore-forming powder and a setting liquid; and immersing said shaped article in an immersing liquid for a period of time so that said pore-forming powder is dissolved in the immersing liquid, creating pores in said shaped article. In addition to the above-mentioned Item 4, the porous hardened CPC article made according to the present invention has the following features and advantages:

- The porous hardened CPC article can transform into an apatite-dominated material shortly after immersion in physiological solution or after implantation.

- The porous hardened CPC article exhibits a higher strength than most other bioactive or biodegradable porous blocks with a similar porosity level.

Brief Description of the Drawings

Figs. 1a to 1d show schematic cross sectional views of four different designs of prosthetic bone implants constructed according to the present invention.

Figs. 2a to 2f are schematic cross sectional views showing steps of a method for preparing a prosthetic bone implant according to one embodiment of the present invention.

Figs. 3a and 3b are schematic vertical and horizontal cross sectional views of a prosthetic bone implant prepared according to another embodiment of the present invention, respectively.

Detailed Description of the Invention

The present invention discloses a method for making a hardened molded calcium phosphate cement (CPC) article comprising impregnating a rigid shaped article of calcium phosphate with an impregnating liquid for a period of time so that a compressive strength of the resulting impregnated article removed from the impregnating liquid is increased compared to that of the rigid shaped article without said impregnating treatment.

Preferably, the impregnating liquid is an acidic solution, a basic solution, a physiological solution, an organic solvent, or a substantially pure water. Preferably, the impregnating liquid comprises at least one of Ca and P sources. Preferably, the impregnating liquid is a Hanks' solution, a HCl aqueous solution or an aqueous solution of $(NH_4)_2HPO_4$.

Preferably, the rigid shaped article of calcium phosphate is a molded article from a paste of calcium phosphate cement.

Preferably, the impregnating is carried out for a period longer than 10 minutes, and more preferably for about 12 hours to 96 hours.

Preferably, the impregnating is carried out 30-90°C, and more preferably at room temperature.

According to a first preferred embodiment of the present invention, a method for making a molded calcium phosphate article comprises the following steps:

(a) preparing a powder of a calcium phosphate cement;

(b) mixing said powder with a setting liquid to form a paste, wherein said paste undergoes a hardening reaction;

(c) molding said paste into an article in a mold of a desired shape and size before said hardening reaction is complete;

(d) impregnating the resulting hardened article from step (c) with an impregnating liquid to allow strength of said article to increase; and

(e) removing said article from said impregnating liquid.

Preferably, said calcium phosphate cement comprises at least one Ca source and at least one P source, or more preferably at least one calcium phosphate source. Said calcium phosphate source comprises one or more calcium phosphates selected from the group consisting of alpha-tricalcium phosphate (α-TCP), beta-tricalcium phosphate (β-TCP), tetracalcium phosphate (TTCP), monocalcium phosphate monohydrate (MCPM), monocalcium phosphate anhydrous (MCPA), dicalcium phosphate dihydrate (DCPD), dicalcium phosphate anhydrous (DCPA), octacalcium phosphate (OCP), calcium dihydrogen phosphate, calcium dihydrogen phosphate hydrate, acid calcium pyrophosphate, anhydrous calcium hydrogen phosphate, calcium hydrogen phosphate hydrate, calcium pyrophosphate, calcium triphosphate, calcium phosphate tribasic, calcium polyphosphate, calcium metaphosphate, anhydrous tricalcium phosphate, tricalcium phosphate hydrate, and amorphous calcium phosphate.

Preferably, the calcium phosphate source comprises at least one calcium phosphate particle having calcium phosphate whiskers on the surface of said calcium phosphate particle, wherein said calcium phosphate whiskers have a length of about 1-5000 nm and a width of about 1-500 nm.

Preferably, the setting liquid in step (b) is an acidic solution, a basic solution, or a substantially pure water.

An acidic solution suitable for use in the present invention is selected from the group consisting of nitric acid (HNO_3), hydrochloric acid (HCl), phosphoric acid (H_3PO_4), carbonic acid (H_2CO_3), sodium dihydrogen phosphate (NaH_2PO_4), sodium dihydrogen phosphate monohydrate ($NaH_2PO_4 \cdot H_2O$), sodium dihydrogen phosphate dihydrate, sodium dihydrogen phosphate dehydrate, potassium dihydrogen phosphate (KH_2PO_4), ammonium dihydrogen phosphate ($NH_4H_2PO_4$), malic acid, acetic acid, lactic acid, citric acid, malonic acid, succinic acid, glutaric acid, tartaric acid, oxalic acid and their mixture.

A basic solution suitable for use in the present invention is selected from the group consisting of ammonia, ammonium hydroxide, alkali metal hydroxide, alkali earth hydroxide, disodium hydrogen phosphate (Na_2HPO_4), disodium hydrogen phosphate dodecahydrate, disodium hydrogen phosphate heptahydrate, sodium phosphate dodecahydrate ($Na_3PO_4 \cdot 12H_2O$), dipotassium hydrogen phosphate (K_2HPO_4), potassium hydrogen phosphate trihydrate ($K_2HPO_4 \cdot 3H_2O$), potassium phosphate tribasic (K_3PO_4), diammonium hydrogen phosphate ($(NH_4)_2HPO_4$), ammonium phosphate trihydrate ($(NH_4)_3PO_4 \cdot 3H_2O$), sodium hydrogen carbonate ($NaHCO_3$), sodium carbonate Na_2CO_3, and their mixture.

Step (c) of the method of the present invention preferably further comprises removing said article from said mold.

Step (c) of the method of the present invention preferably further comprises removing a portion of liquid from said paste, so that a liquid/powder ratio of said paste decreases.

Step (c) of the method of the present invention preferably further comprises pressurizing said paste in said mold, preferably between 1 and 500 MPa, before said hardening reaction is complete to remove a portion of liquid from said paste, so that a liquid/powder ratio of said paste decreases. More preferably, step (c) further comprises heating said paste during said pressurizing.

Step (c) of the method of the present invention preferably further comprises heating said paste during molding.

Step (d) of the method of the present invention preferably further comprises heating the impregnating liquid, preferably at a temperature between 30 and 90°C during said impregnating.

The method of the present invention may further comprise drying said article after removing said article from said impregnating liquid.

The method of the present invention may further comprise heating said article, preferably at a temperature between 50 and 500°C, after removing said article from said impregnating liquid.

The molded calcium phosphate article made according to the method of the present invention may be used as a medical implant or a reinforcing constituent of a composite.

According to a second preferred embodiment of the present invention, a method for making a porous hardened CPC article is provided. The second preferred embodiment is similar to the first embodiment with a major difference in that a pore-forming powder is mixed with the powder of calcium phosphate cement used in step (a). The method for making a porous hardened CPC article according to the second preferred embodiment comprises:

i) preparing a shaped article from a paste comprising a calcium phosphate cement, a pore-forming powder and a setting liquid;

ii) immersing said shaped article in an immersing liquid for a first period of time so that said pore-forming powder is dissolved in the immersing liquid, creating pores in said shaped article;

iii) removing the resulting porous shaped article from said immersing liquid; and

iv) immersing the porous shaped article from step iii) in an impregnating liquid for a second period of time so that a compressive strength of the resulting article removed from the impregnating liquid is increased compared to that of said porous shaped article without said impregnating treatment,

wherein step iii) is omitted and a compressive strength of the resulting porous shaped article removed from the immersing liquid after the first and the second periods of time is increased compared to that of the resulting porous shaped article removed after the first period of time, when the immersing liquid and the impregnating liquid are the same.

Said pore-forming powder preferably is selected from the group consisting of LiCl, KCl, NaCl, $MgCl_2$, $CaCl_2$, $NaIO_3$, KI, Na_3PO_4, K_3PO_4, Na_2CO_3, amino acid-sodium salt, amino acid-potassium salt, glucose, polysaccharide, fatty acid-sodium salt, fatty acid-potassium salt, potassium bitartrate ($KHC_4H_4O_6$), potassium carbonate, potassium gluconate ($KC_6H_{11}O_7$), potassium-sodium tartrate ($KNaC_4H_4O_6 \cdot 4H_2O$), potassium sulfate (K_2SO_4), sodium sulfate, and sodium lactate.

Preferably, said immersing liquid in step ii) and said impregnating liquid in step iv) independently are an acidic aqueous solution, a basic aqueous solution, a physiological solution, an organic solvent, or a substantially pure water. Said immersing liquid may comprises at least one of Ca and P sources. Said immersing liquid may be a Hanks' solution, a HCl aqueous solution or an aqueous solution of $(NH_4)_2HPO_4$.

Said impregnating liquid in step iv) may be different from or the same as the immersing liquid in step i).

Preferably, the first period of time in step ii) is longer than 10 minutes, and more preferably longer than 1 day.

Preferably, the second period of time in step iv) is longer than 10 minutes, and more preferably longer than 1 day.

Preferably, the immersing in step ii) and iv) is carried out at room temperature or at a temperature between about 30 and 90°C.

Preferably, said paste in step i) further comprises living cells.

Preferably, said immersing liquid in step ii) comprises living cells.

Preferably, said impregnating liquid in step iv) comprises living cells.

Preferably, said porous shaped article having an increased compressive strength removed from said impregnating liquid in step iv) has a porosity of at least 20 vol%, and more preferably of 40-90 vol%.

The porous hardened CPC article made according to the method of the present invention may be used as a tissue-engineered scaffold, medical implant or a reinforcing constituent of a composite.

According to a third preferred embodiment of the present invention, a method for making a dual function hardened CPC article for use as a prosthetic bone implant is provided. The third preferred embodiment basically is a combination of the first embodiment and the second embodiment, wherein a first CPC paste without the pore-forming powder and a second CPC paste containing the pore-forming powder are used to mold an integral article and immersing the integral article in the impregnating liquid, so that the pore-forming powder is dissolved in the immersing liquid, creating pores in the integral article while the hardened CPC gaining compressive strength. Features of the third preferred embodiments of the present invention includes (but not limited to) the following:

1. A prosthetic bone implant comprising a cortical portion having two opposite sides, and a cancellous portion integrally disposed in said cortical portion and being exposed through said two opposite sides, wherein said cortical portion comprises a hardened calcium phosphate cement has a porosity of less than 40% in volume, and said cancellous portion comprises a porous hardened calcium phosphate cement having a porosity greater than 20% in volume, and greater than that of said cortical portion.
2. The prosthetic bone implant according to Feature 1, wherein the cortical portion is in the form of a hollow disk, and the cancellous portion is in the form of a column surrounded by the hollow disk.
3. The prosthetic bone implant according to Feature 2 further comprising a transitional portion between said column and said hollow disk surrounding said central cylinder, which has properties range from those of said cancellous portion to said cortical portion.
4. The prosthetic bone implant according to Feature 1, wherein the cortical portion is in the form of a disk having one or more longitudinal through holes, and the cancellous portion is in the form of one or more columns surrounded by said one or more longitudinal through holes.
5. The prosthetic bone implant according to Feature 1, wherein said hardened calcium phosphate cement of said cortical portion comprises an apatitic phase as a major phase giving rise to broadened characteristic X-ray diffraction peaks in comparison with a high-temperature sintered apatitic phase.
6. The prosthetic bone implant according to Feature 5, wherein said broadened characteristic the X-ray diffraction peaks are at 2-Theta values of 25-27° and 30-35°.
7. The prosthetic bone implant according to Feature 1, wherein said hardened calcium phosphate cement of said cortical portion is prepared without a high temperature sintering.
8. The prosthetic bone implant according to Feature 1, wherein said hardened calcium phosphate cement of said cortical portion comprises an apatitic phase as a major phase having a Ca/P molar ratio of 1.5-2.0.
9. The prosthetic bone implant according to Feature 1, wherein said hardened calcium phosphate cement of said cancellous portion comprises an apatitic phase as a major phase giving rise to broadened characteristic X-ray diffraction peaks in comparison with a high-temperature sintered apatitic phase.
10. The prosthetic bone implant according to Feature 9, wherein said broadened characteristic the X-ray diffraction peaks are at 2-Theta values of 25-27° and 30-35°.
11. The prosthetic bone implant according to Feature 1, wherein said hardened calcium phosphate cement of said cancellous portion is prepared without a high temperature sintering.
12. The prosthetic bone implant according to Feature 1, wherein said hardened calcium phosphate cement of said

cancellous portion comprises an apatitic phase as a major phase having a Ca/P molar ratio of 1.5-2.0.

13. The prosthetic bone implant according to Feature 1, wherein said cortical portion comprises 10-90% in volume of said implant.
14. The prosthetic bone implant according to Feature 1, wherein said cortical portion has a porosity of less than 30% in volume.
15. The prosthetic bone implant according to Feature 1, wherein said cancellous portion has a porosity greater than 40-90% in volume.
16. A method for preparing a prosthetic bone implant comprising a cortical portion having two opposite sides, and a cancellous portion integrally disposed in said cortical portion and being exposed through said two opposite sides, said method comprises the following steps:
    a) preparing a first paste comprising a first calcium phosphate cement and a first setting liquid;
    b) preparing a second paste comprising a second calcium phosphate cement, a pore-forming powder and a second setting liquid;
    c) i) preparing a shaped article in a mold having two or more cells separated by one more partition walls comprising introducing said first paste and said second paste into said two or more cells separately, and removing said one or more partition walls from said mold, so that said second paste in the form of a single column or two or more isolated columns is integrally disposed in the first paste in said mold; or ii) preparing a shaped article comprising introducing one of said first paste and said second paste into a first mold to form an intermediate in said first mold, placing said intermediate into a second mold after a hardening reaction thereof undergoes at least partially, and introducing another one of said first paste ad said second paste into said second mold, so that said second paste as a single column or as two or more isolated columns is integrally disposed in the first paste in said second mold;
    d) immersing the resulting shaped article from step c) in an immersing liquid for a first period of time so that said pore-forming powder is dissolved in the immersing liquid, creating pores in said single column or said two or more isolated columns; and
    e) removing the immersed shaped article from said immersing liquid.
17. The method according to Feature 16 further comprising
    f) drying the immersed shaped article.
18. The method according to Feature 16, wherein said pore-forming powder is the same as that used in the second preferred embodiment of the present invention.
19. The method according to Feature 16, wherein said first calcium phosphate cement comprises at least one Ca source and at least one P source, or at least one calcium phosphate source; and said second calcium phosphate cement comprises at least one Ca source and at least one P source, or at least one calcium phosphate source.
20. The method according to Feature 19, wherein said first calcium phosphate cement comprises at least one calcium phosphate source, and said second calcium phosphate cement comprises at least one calcium phosphate source.
21. The method according to Feature 20, wherein said calcium phosphate source is the same as that used in the first preferred embodiment of the present invention.
22. The method according to Feature 21, wherein said first calcium phosphate cement and said second calcium phosphate cement are identical.
23. The method according to Feature 22, wherein said first calcium phosphate cement and said second calcium

phosphate cement are tetracalcium phosphate.

24. The method according to Feature 16, wherein the first setting liquid and the second setting liquid independently are an acidic solution, a basic solution, or a substantially pure water.
25. The method according to Feature 24, wherein said acidic solution is the same as that used in the first preferred embodiment of the present invention.
26. The method according to Feature 22, wherein said basic solution is the same as that used in the first preferred embodiment of the present invention.
27. The method according to Feature 16, wherein step c-i) further comprises allowing said first paste and said second paste undergoing a hardening reaction in said mold.
28. The method according to Feature 16, wherein step c-i) further comprises pressurizing said first paste and said second paste in said mold after removing said one or more partition walls from said mold to remove a portion of liquid from said first paste and said second paste, so that a liquid/powder ratio of said first paste and of said second paste decreases; and allowing said first paste and second paste undergoing a hardening reaction in said mold.
29. The method according to Feature 16, wherein step c-ii) further comprises allowing said intermediate undergoing a hardening reaction in said first mold, and allowing said another one of said first paste and said second paste undergoing a hardening reaction in said second mold.
30. The method according to Feature 16, wherein step c-ii) further comprises pressurizing said one of said first paste and said second paste in said first mold to remove a portion of liquid therefrom before the hardening reaction of said intermediate is completed; allowing said intermediate undergoing a hardening reaction in said first mold; pressuring said another one of said first paste and said second paste in said second mold, so that a liquid/powder ratio of said another one of said first paste and of said second paste decreases; and allowing said another one of said first paste and second paste undergoing a hardening reaction in said second mold.
31. The method according to Feature 28, wherein said pressuring is about 1 to 500 MPa.
32. The method according to Feature 30, wherein said pressuring is about 1 to 500 MPa.
33. The method according to Feature 16, wherein the immersing liquid is an acidic aqueous solution, a basic aqueous solution, a physiological solution, an organic solvent, or a substantially pure water.
34. The method according to Featur 33, wherein the immersing liquid comprises at least one of Ca and P sources.
35. The method according to Feature 33, wherein the immersing liquid is a Hanks' solution, a HCl aqueous solution or an aqueous solution of $(NH_4)_2HPO_4$.
36. The method according to Feature 16, wherein the immersing in step d) is carried out for a period longer than 10 minutes.
37. The method according to Feature 16, wherein the immersing in step d) is carried out for a period longer than 1 day.
38. The method according to Feature 16, wherein the immersing in step d) is carried out at a temperature of about 10 and 90°C.
39. The method according to Feature 38, wherein the immersing in step d) is carried out at room temperature.
40. The method according Feature 17 further comprising cleaning said immersed shaped article before said drying; and heating the resulting dried shaped article at a temperature between 50 and 500°C.

Four different designs of prosthetic bone implants constructed according to the present invention are shown in Figs. 1a to 1d. In Fig. 1a, the prosthetic bone implant of the present invention has a dense cortical

portion D1 in the tubular form and a porous cancellous portion P1 formed in the central through hole of the tubular cortical portion D1. Both the dense cortical portion D1 and the porous cancellous portion P1 are made of a hardened calcium phosphate cement having an apatitic phase as a major phase. In Fig. 1b, the prosthetic bone implant of the present invention has a dense cortical portion D1 in the tubular form; a cylindrical porous cancellous portion P1 in the center of the tubular cortical portion D1; and an annular transitional portion P2 connecting the tubular cortical portion D1 and the cylindrical cancellous portion P1. The transitional portion P2 is made of a hardened calcium phosphate cement having an apatitic phase as a major phase, and a porosity gradient increasing from the lower porosity of the cylindrical cancellous portion P1 to the higher porosity of the tubular cortical portion D1, which may be formed in-situ during molding of two different two different CPC pastes, one of them having an additional pore-forming powder for forming the cylindrical cancellous portion P1, and another one being a regular CPC powder for forming the dense cortical portion D1. The porous cancellous portion P1 may be in the forms of isolated columns surrounded by the dense cortical portion D1 as shown in Figs. 1c and 1d. Other designs are also possible in addition to those shown in Figs. 1a to 1d.

A suitable method for preparing the prosthetic bone implant of the present invention includes placing a tubular partition wall 10 in a hollow cylindrical mold 20, as shown in Fig. 2a; pouring a first paste comprising a calcium phosphate cement and a setting liquid in the annular cell and a second paste comprising the calcium phosphate cement, a pore-forming powder and the setting liquid in the central cell, as shown in Fig. 2b; removing the partition wall and pressing the CPC pastes before hardening, as shown in Fig. 2c, wherein a portion of the setting liquid is removed from the gap between the mold 20 and the press 30 and/or holes (not shown in the drawing) provided on the press 30. The CPC paste will undergo a hardening reaction to convert into apatitic phase. The hardened disk is removed from the mold and is subjected to surface finishing to expose the central portion hardened from the second paste, as shown in Fig. 2d, followed by immersing in a bath of an immersing liquid as shown in Fig. 2e, where the pore-forming powder is dissolved in the immersing liquid while the hardened CPC thereof gaining compressive strength. The immersing may last from 10 minutes to several days. The composite disk so formed is washed with water after being removed from the bath, and dried and heated in an oven to obtain the prosthetic bone implant as shown in Fig. 2f. The heating is conducted at a temperature between 50 and 500°C for a period of several hours to several days, which enhance the compressive strength of the cortical portion of the prosthetic bone implant.

An alternative method for preparing the prosthetic bone implant of the present invention from the same raw materials includes pouring the second paste in a first mold, pressing the second paste to remove a portion of the setting liquid from the second paste before the hardening reaction is completed, so that the liquid/powder ratio in the second paste decreases, and allowing the hardening reaction undergo in the mold for a period of time, e.g. 15 minutes starting from the mixing of the CPC powder, the pore-forming powder and the setting liquid, to obtain a cylindrical block having a diameter of 7 mm. Then, the cylindrical block is removed from the first mold, and placed in the center of a second mold having a diameter of 10 mm. The first paste is poured into the annular space in the second mold, and a press having a dimension corresponding to the annular shape is used to pressure the first paste to remove a portion of the setting liquid from the first paste before the hardening reaction is completed, so that the liquid/powder ratio in the first paste decreases. Again, the first paste will undergo a hardening reaction to convert into apatitic phase. The hardened cylinder having a diameter of 10 mm is removed from the second mold, followed by immersing in an immersing liquid, where the pore-forming powder contained in the second paste is dissolved in the immersing liquid while the hardened CPC thereof gaining compressive strength, to obtain the

prosthetic bone implant of the present invention, as shown in Figs. 3a and 3b. It is apparently to people skilled in the art that the prosthetic bone implant shown in Figs. 3a and 3b can also be prepared by changing the sequence of the molding of the first paste and the second paste with modifications to the second mold used in this alternative method.

The following examples are intended to demonstrate the invention more fully without acting as a limitation upon its scope, since numerous modifications and variations will be apparent to those skilled in this art.

PREPARATIVE EXAMPLE 1: Preparation of TTCP Powder

A $Ca_4(PO_4)_2O$ (TTCP) powder was prepared by mixing $Ca_2P_2O_7$ powder with $CaCO_3$ powder uniformly in ethanol for 24 hours followed by heating to dry. The mixing ratio of $Ca_2P_2O_7$ powder to $CaCO_3$ powder was 1:1.27 (weight ratio) and the powder mixture was heated to 1400°C to allow two powders to react to form TTCP.

PREPARATIVE EXAMPLE 2: Preparation of conventional TTCP/DCPA-based CPC powder (abbreviated as C-CPC)

The resulting TTCP powder from PREPARATIVE EXAMPLE 1 was sieved and blended with dried $CaHPO_4$ (DCPA) powder in a ball mill for 12 hours. The blending ratio of the TTCP powder to the DCPA powder was 1:1 (molar ratio) to obtain the conventional CPC powder. Particles of this C-CPC powder have no whisker on the surfaces thereof.

PREPARATIVE EXAMPLE 3: Preparation of non-dispersive TTCP/DCPA-based CPC powder (abbreviated as ND-CPC)

The TTCP powder prepared according to the method of PREPARATIVE EXAMPLE 1 was sieved and blended with dried $CaHPO_4$ (DCPA) powder in a ball mill for 12 hours. The blending ratio of the TTCP powder to the DCPA powder was 1:1 (molar ratio). The resultant powder mixture was added to a 25 mM diluted solution of phosphate to obtain a powder/solution mixture having a concentration of 3 g powder mixture per 1 ml solution while stirring. The resulting powder/solution mixture was formed into pellets, and the pellets were heated in an oven at 50°C for 10 minutes. The pellets were then uniformly ground in a mechanical mill for 20 minutes to obtain the non-dispersive TTCP/DCPA-based CPC powder (ND-CPC). The particles of this ND-CPC powder have whisker on the surfaces thereof.

Dense blocks

EXAMPLE 1: Effect of immersion time on compressive strength of CPC block

To a setting solution of 1M phosphoric acid solution (pH = 5.89) the ND-CPC powder from PREPARATIVE EXAMPLE 3 was added in a liquid/powder ratio (L/P ratio) of 0.4, i.e. 4 ml liquid/10 g powder, while stirring. The resulting paste was filled into a cylindrical steel mold having a length of 12 mm and a diameter of 6 mm, and was compressed with a gradually increased pressure until a maximum pressure was reached. The maximum pressure was maintained for one minute, and then the compressed CPC block was removed from the mold. At the 15^{th} minute following the mixing of the liquid and powder, the compressed CPC block was immersed in a Hanks' solution for 1 day, 4 days, and 16 days. Each test group of the three different periods of immersion time has five specimens, the compressive strength of which was measured by using a AGS-500D mechanical tester (Shimadzu Co., Ltd., Kyoto, Japan) immediately following the removal thereof from the Hanks'

solution without drying. The CPC paste in the mold was compressed with a maximum pressure of 166.6 MPa, and in the course of the compression the compression speeds were about 5 mm/min during 0~104.1 MPa; 3 mm/min during 104.1~138.8 MPa; 1 mm/min during 138.8~159.6 MPa: and 0.5 mm/min during 159.6~166.6 MPa. The measured wet specimen compressive strength is listed Table 1.

Table 1

Immersion time (Day)	Compressive strength (MPa)	Standard deviation (MPa)
No immersion	37.3*	0.6
1 day	149.2	12.9
4 days	122.7	6.7
16 days	116.4	7.7

*This value was measured before the compressed CPC blocks were immersed in the Hanks' solution, and it was substantially the same for the compressed CPC blocks not immersed in the Hanks' solution measured a few days after the preparation.

It can seen from Table 1 that the compressive strength of the compressed CPC blocks is increased remarkably after one-day immersion in comparison with the non-immersed block, and declines a little for a longer immersion time.

EXAMPLE 2: Effect of whiskers on compressive strength of TTCP/DCPA-based CPC block

The procedures of EXAMPLE 1 were repeated by using the C-CPC powder prepared in PREPARATIVE EXAMPLE 2 and the ND-CPC powder prepared in PREPARATIVE EXAMPLE 3. The maximum pressure used to compress the CPC paste in the mold in this example was 156.2 MPa. The results for one-day immersion time are listed in Table 2.

Table 2

CPC powder	Compressive strength (MPa)	Standard deviation (MPa)
C-CPC (no whisker)	62.3	5.0
ND-CPC (with whisker)	138.0	8.2

It can be seen from Table 2 that the compressive strength, 62.3 MPa, of the immersed compressed CPC block prepared from the conventional CPC powder (no whisker) is about 1.7 times of that (37.3 MPa) of the non-immersed compressed CPC block in Table 1, and the compressive strength, 138.0 MPa, of the immersed compressed CPC block prepared from the non-dispersive CPC powder (with whisker) is about 3.7 times of that of the non-immersed compressed CPC block in Table 1

EXAMPLE 3: Effect of whiskers on compressive strength of TTCP-based CPC block

$Ca_4(PO_4)_2O$ (TTCP) powder as synthesized in PREPARATIVE EXAMPLE 1 was sieved with a #325 mesh. The sieved powder has an average particle size of about 10 μm. To the TTCP powder HCl aqueous solution (pH = 0.8) was added according to the ratio of 1g TTCP/13ml solution. The TTCP powder was immersed in the HCl aqueous solution for 12 hours, filtered rapidly and washed with deionized water, and filtered rapidly with a vacuum

pump again. The resulting powder cake was dried in an oven at 50°C. The dried powder was divided into halves, ground for 20 minutes and 120 minutes separately, and combined to obtain the non-dispersive TTCP-based CPC powder, the particles of which have whisker on the surfaces thereof. A setting solution of diammonium hydrogen phosphate was prepared by dissolving 20 g of diammonium hydrogen phosphate, $(NH_4)_2HPO_4$, in 40 ml deionized water. The procedures in EXAMPLE 1 were used to obtain the wet specimen compressive strength for one-day immersion time, wherein the maximum pressure to compress the CPC paste in the mold was 156.2 MPa. The results are shown in Table 3.

Table 3

CPC powder	Compressive strength (MPa)	Standard deviation (MPa)
TTCP (no whisker)	79.6	8.8
TTCP (with whisker)	100	4.2

The trend same as the TTCP/DCPA-based CPC powder in Table 2 of EXAMPLE 2 can be observed in Table 3.

EXAMPLE 4: Effect of molding pressure on compressive strength of ND-CPC block (in low pressure regime: 0.09~3.5 MPa)

The procedures of EXAMPLE 1 were repeated except that the maximum pressure used to compress the CPC paste in the mold was changed from 166.6 MPa to the values listed in Table 4. The period of immersion was one day. The results are listed in Table 4.

Table 4

Pressure for compressing the CPC paste in mold (MPa)	Compressive strength (MPa)	Standard deviation (MPa)
0.09	12.3	2.0
0.35	16.0	2.3
0.7	20.7	2.5
1.4	26.4	1.4
3.5	35.2	3.7

The data in Table 4 indicate that the compressive strength of the CPC block increases as the pressure used to compress the CPC paste in the mold increases.

EXAMPLE 5: Effect of reducing liquid/powder ratio during compression of the CPC paste in the mold on compressive strength of ND-CPC block

The procedures of EXAMPLE 1 were repeated except that the maximum pressure used to compress the CPC paste in the mold was changed from 166.6 MPa to the values listed in Table 5. The liquid leaked from the mold during compression was measured, and the liquid/powder ratio was re-calculated as shown in Table 5. The period of immersion was one day. The results are listed in Table 5.

Table 5

Pressure for compressing the CPC paste in mold (MPa)	L/P ratio (after a portion of liquid removed)	Compressive strength (MPa)	Standard deviation (MPa)
1.4	0.25	26.4	1.4
34.7	0.185	75.3	3.9
69.4	0.172	100.4	6.8
156.2	0.161	138.0	8.2
166.6	0.141	149.2	12.9

The data in Table 5 show that the compressive strength of the CPC block increases as the liquid/powder ratio decreases during molding.

EXAMPLE 6: Effect of post-heat treatment on compressive strength of CPC block

The procedures of EXAMPLE 1 were repeated. The period of immersion was one day. The CPC blocks after removing from the Hanks' solution were subjected to post-heat treatments: 1) 50°C for one day; and 2) 400°C for two hours with a heating rate of 10°C per minute. The results are listed in Table 6.

Table 6

	Compressive strength (MPa)	Standard deviation (Mpa)
No post-heat treatment	149.2	12.9
50°C, one day	219.4	16.0
400°C, two hours	256.7	16.2

It can be seen from Table 6 that the post-heat treatment enhances the compressive strength of the CPC block.

Porous blocks

EXAMPLE 7: Effect of KCl content and immersion time on compressive strength of porous CPC block

To a setting solution of 1M phosphoric acid solution (pH = 5.89) the ND-CPC powder from PREPARATIVE EXAMPLE 3 was added in a liquid/powder ratio (L/P ratio) of 0.4, i.e. 4 ml liquid/10 g powder, while stirring. KCl powder in a predetermined amount was mixed to the resulting mixture by stirring intensively. The resulting paste was filled into a cylindrical steel mold having a length of 12 mm and a diameter of 6 mm, and was compressed with a gradually increased pressure until a maximum pressure of 3.5 MPa was reached. The maximum pressure was maintained for one minute, and then the compressed CPC block was removed from the mold. At the 15th minute following the mixing of the liquid and powders, the compressed CPC block was immersed in a deionized water at 37°C for 4 days, 8 days, and 16 days. The compressive strength of the specimens of the three different periods of immersion time was measured by using a AGS-500D mechanical tester (Shimadzu Co., Ltd., Kyoto, Japan) after the specimens were dry. The measured dry specimen compressive strength is listed Table 7.

Table 7

KCl/CPC ratio by weight \ Immersion time (Day)	Dry compressive strength (MPa)		
	4 days	8 days	16 days
1	7.0	5.4	6.6
1.5	3.9	2.7	4.3
2	1.3	2.3	2.6

It can seen from Table 7 that the dry compressive strength of the porous CPC blocks decreases as the KCl/CPC ratio by weight increases.

EXAMPLE 8: Porosity and compressive strength of porous CPC blocks prepared from different pore-forming powders

The procedures of EXAMPLE 7 were repeated by using sugar, KI, $C_{17}H_{33}COONa$ and $C_{13}H_{27}COOH$ instead of KCl. The immersion time was 14 days in deionized water. In the cases where the $C_{17}H_{33}COONa$ and $C_{13}H_{27}COOH$ were used, the CPC blocks were further immersed in ethanol for additional four days. The conditions and the results are listed in Table 8.

Table 8

Pore-forming powder	S[a)]	C.S. (MPa)[b)]	Porosity (vol %)[c)]
Sugar	1	4.1	58.4
KI	2	4.3	62.2
KI	3	1.7	75.5
C17H33COONa	1	8.0	56.0
C13H27COOH	2	5.9	60.1

[a)] S = Pore-forming powder/CPC by volume.

b) C.S. = dry compressive strength (hereinafter abbreviated as C.S.).

c) Porosity: Porosity (vol%) was measured by Archimedes' method, and calculated as in ASTM C830.

It can be seen from Table 8 that various powders which are soluble in water can be used in the preparation of a porous CPC block according to the method of the present invention.

Dual-Functional block

Example 9

To a setting solution of 1M phosphoric acid solution (pH = 5.89) the ND-CPC powder from PREPARATIVE EXAMPLE 3 was added in a liquid/powder ratio (L/P ratio) of 0.4, i.e. 4 ml liquid/10 g powder, while stirring. KCl powder in a ratio of KCl powder/CPC by volume of 2 was mixed to the resulting mixture by stirring intensively. The resulting paste was filled into a cylindrical steel mold having a length of 12 mm and a diameter of 7 mm, and was compressed with a gradually increased pressure until a maximum pressure of 3.5 MPa was reached. The maximum pressure was maintained for one minute, and then the compressed CPC block was removed from the mold at the 15th minute following the mixing of the liquid and powders.

The resulting cylinder having a diameter of 7 mm was placed in another cylindrical steel mold having a diameter of 10 mm. To a setting solution of 1M phosphoric acid solution (pH = 5.89) the ND-CPC powder from PREPARATIVE EXAMPLE 3 was added in a liquid/powder ratio (L/P ratio) of 0.4, i.e. 4 ml liquid/10 g powder, while stirring. The resulting paste was filled into the gap between said cylinder and said another mold, and was compressed with a gradually increased pressure until a maximum pressure of 50 MPa was reached. The maximum pressure was maintained for one minute. At the 15th minute following the mixing of the liquid and ND-CPC powder, the CPC/KCl composite block was immersed in a deionized water at 37°C for 4 days. KCl powder was dissolved in the deionized water, and a dual-functional CPC block having a porous CPC cylinder surround by a dense CPC annular block was obtained.

The compressive strength of the specimen was measured by using a AGS-500D mechanical tester (Shimadzu Co., Ltd., Kyoto, Japan) after the specimens were dry. The measured dry specimen compressive strength is 68.8 MPa.

The porosities of the porous CPC cylinder and the dense CPC annular block were measured by Archimedes' method, and calculated as in ASTM C830, after the dual-functional CPC block was broken intentionally, and the results are 74% and 30%, respectively.

X-ray diffraction pattern of the powder obtained by grinding the dual-functional CPC block shows broadened characteristic X-ray diffraction peaks of apatite at $2\theta = 25\text{-}27°$ and $2\theta = 20\text{-}35°$ with a scanning range of 2θ of 20-40° and a scanning rate of 1°/min. The results indicate that the powder is a mixture of apatite and TTCP with apatite as a major portion.

Although the present invention has been described with reference to specific details of certain embodiments thereof, it is not intended that such details should be regarded as limitations upon the scope of the invention except as and to the extent that they are included in the accompanying claims. Many modifications and variations are possible in light of the above disclosure

WHAT IS CLAIMED IS:

1. A prosthetic bone implant comprising:
a load bearing component; and
a plurality of porous components substantially surrounded by the load bearing component;
wherein the load bearing component and the porous component comprise a hardened calcium phosphate cement, wherein the prosthetic bone implant is at least partially bioresorbable over time, and wherein the load bearing component has a greater compressive strength than the porous component.

2. The prosthetic bone implant as claimed in claim 1, wherein the porosity of the porous component is greater than the porosity of the load bearing component.

3. The prosthetic bone implant as claimed in any of claims 1 or 2, wherein the porosity of the porous component is from about 20 % by volume to about 90 % by volume.

4. The prosthetic bone implant as claimed in any of claims 1-3, wherein the porosity of the load bearing component is less than about 30% by volume.

5. The prosthetic bone implant as claimed in any of claims 1-4, wherein the load-bearing component is adapted to withstand a compressive force of: greater than about 35 MPa; from about 35 MPa to about 250 MPa, or from about 110 MPa to about 170 MPa.

6. The prosthetic bone implant as claimed in any of claims 1-5, wherein the hardened calcium phosphate cement of the load bearing component and the hardened calcium phosphate cement of the porous component is made from at least one calcium phosphate source.

7. The prosthetic bone implant as claimed in claim 6, wherein the calcium phosphate source comprises alpha-tricalcium phosphate (α-TCP), beta- tricalcium phosphate (β-TCP), tetracalcium phosphate (TTCP), monocalcium phosphate monohydrate (MCPN), monocalcium phosphate anhydrous (MCPA), dicalcium phosphate dihydrate (DCPD), dicalcium phosphate anhydrous (DCPA), octacalcium phosphate (OCP), calcium dihydrogen phosphate, calcium dihydrogen phosphate hydrate, acid calcium pyrophosphate, anhydrous calcium hydrogen phosphate, calcium hydrogen phosphate hydrate, calcium pyrophosphate, calcium triphosphate, calcium phosphate tribasic, calcium polyphosphate, calcium metaphosphate, anhydrous tricalcium phosphate, tricalcium phosphate hydrate, amorphous calcium phosphate, or mixtures thereof.

8. The prosthetic bone implant as claimed in claim 6, wherein at least a portion of the hardened calcium phosphate cement of the load bearing component and at least a portion of the hardened calcium phosphate cement of the porous component is made from tetracalcium phosphate.

9. The prosthetic bone implant as claimed in claim 6, wherein at least a portion of the hardened calcium phosphate cement of the load bearing component and at least a portion of the hardened calcium phosphate cement of the porous component is made from tetracalcium phosphate and dicalcium phosphate anhydrous.

10. The prosthetic bone implant as claimed in claim 6, wherein at least a portion of the hardened calcium phosphate cement of the load bearing component and at least a portion of the hardened calcium phosphate cement of the porous component is made from tetracalcium phosphate, wherein at least a portion of tetracalcium phosphate particles comprises whiskers on the surface of the tetracalcium phosphate particles.

11. The prosthetic bone implant as claimed in any of claims 1-10, wherein at least a portion of the hardened calcium phosphate cement of the load bearing component and at least a portion of the hardened calcium phosphate cement of the porous component is made from apatite.

12. The prosthetic bone implant as claimed in claim 11, wherein the molar ratio of calcium/phosphate of the apatite is about 1.5 to about 2.0.

13. The prosthetic bone implant as claimed in any of claims 1-12, further comprising a transitional component coupling one or more porous components to the load bearing component, the transitional component comprising a hardened calcium phosphate cement.

14. The prosthetic bone implant as claimed in claim 13, wherein the transitional component comprises a porosity gradient increasing from the porosity of the porous component to the porosity of the load bearing component.

15. The prosthetic bone implant as claimed in any of claims 1-14, wherein the porous components are substantially surrounded by the load-bearing component.

16. A method of forming a prosthetic bone implant comprising:

adding a porous component paste to a first mold, wherein the porous component paste comprises at least one calcium phosphate cement combined with at least one pore forming agent and at least one setting agent to form a porous component;

adding one or more porous components and a load bearing component paste to a second mold, wherein the load bearing component paste comprises at least one calcium phosphate cement combined with least one setting agent, to form a hardened calcium phosphate article, the hardened calcium phosphate article comprising a load bearing component at least partially surrounding one or more porous components; and

forming the prosthetic bone implant, wherein the prosthetic bone implant comprises the hardened calcium phosphate article.

17. The method as claimed in claim 16, further comprising subjecting the porous component paste to a molding pressure of greater than about 1 MPa or between about 1 MPa to about 500 MPa to form the porous component.

18. The method as claimed in claims 16 or 17, further comprising subjecting the load bearing component paste to a molding pressure of greater than about 1 MPa or about 1MPa to about 500 MPa to form the hardened calcium phosphate article.

19. A method of forming a prosthetic bone implant comprising:

adding a porous component paste to one or more first molds, wherein the porous component paste comprises at least one calcium phosphate cement combined with at least one pore forming agent and at least one setting agent, wherein the first molds are disposed in a second mold;

adding a load bearing component paste to the second mold;

removing one or more of the first molds;

forming a hardened calcium phosphate article, the hardened calcium phosphate article comprising a load bearing component at least partially surrounding one or more porous components; and

forming the prosthetic bone implant, wherein the prosthetic bone implant comprises the immersed hardened calcium phosphate article.

20. The method as claimed in claim 19, further comprising subjecting the load bearing component paste and the porous component paste to a molding pressure of greater than about 1 MPa or about 1MPa to about 500 MPa to form the hardened calcium phosphate article.

21. The method as claimed in any of claims 16-20, further comprising immersing the hardened calcium phosphate article in one or more immersing fluids for a predetermined amount of time.

22. The method as claimed in claim 21, wherein immersion of the hardened calcium phosphate article is carried out at a temperature of from about 10 °C to about 90 °C.

23. The method as claimed in any of claims 21 or 22, wherein the prosthetic bone implant is immersed in at least one immersing liquid for a time period sufficient to remove at least a portion of the pore forming agent from the porous component.

24. The method as claimed in any of claims 21-23, wherein at least one immersing liquid comprises at least one source of calcium and least one source of phosphate.

25. The method as claimed in any of claims 21-23, wherein at least one immersing liquid comprises Hank's solution.

26. The method as claimed in any of claims 21-23, wherein at least one immersing liquid comprises substantially pure water.

27. The method as claimed in any of claims 16-26, wherein the pore-forming agent comprises an inorganic salt.

28. The method as claimed in any of claims 16-26, wherein the pore-forming agent comprises an organic salt.

29. The method as claimed in any of claims 16-28, wherein the porous component paste comprises at least one calcium phosphate source, and the load bearing component paste comprises at least one calcium phosphate source.

30. The method as claimed in claim 29, wherein at least one calcium phosphate source alpha-tricalcium phosphate (α-TCP), beta-tricalcium phosphate (β-TCP), tetracalcium phosphate (TTCP), monocalcium phosphate monohydrate (MCPM), monocalcium phosphate anhydrous (MCPA), dicalcium phosphate dihydrate (DCPD), dicalcium phosphate anhydrous (DCPA), octacalcium phosphate (OCP), calcium dihydrogen phosphate, calcium dihydrogen phosphate hydrate, acid calcium pyrophosphate, anhydrous calcium hydrogen phosphate, calcium hydrogen phosphate hydrate, calcium pyrophosphate, calcium triphosphate, calcium phosphate tribasic, calcium polyphosphate, calcium metaphosphate, anhydrous tricalcium phosphate, tricalcium phosphate hydrate, amorphous calcium phosphate or mixtures thereof.

31. The method as claimed in claim 29, wherein the calcium phosphate source comprises tetracalcium phosphate, wherein at least a portion of the tetracalcium phosphate particles comprise whiskers on the surface of the particles.

32. The method as claimed in any of claims 16-31, wherein at least one of the setting agents comprises substantially pure water.

33. The method as claimed in any of claims 16-31, wherein at least one of the setting agents comprises an acidic solution, and wherein the acidic solution comprises nitric acid (HNO_3), hydrochloric acid (HCl), phosphoric acid (H_3PO_4), carbonic acid (H_2CO_3), sodium dihydrogen phosphate (NaH_2PO_4), sodium dihydrogen phosphate monohydrate ($NaH_2PO_4 \cdot H_2O$), sodium dihydrogen phosphate dihydrate, sodium dihydrogen phosphate dehydrate, potassium dihydrogen phosphate (KH_2PO_4), ammonium dihydrogen.phosphate ($NH_4H_2PO_4$), malic acid, acetic acid, lactic acid, citric acid, malonic acid, succinic acid, glutaric acid, tartaric acid, oxalic acid or mixtures thereof.

34. The method as claimed in any of claims 16-31, wherein at least one of the setting agents comprises a basic solution, and wherein the basic solution comprises ammonia, ammonium hydroxide, alkali metal hydroxide, alkali earth hydroxide, disodium hydrogen phosphate (Na_2HPO_4), disodium hydrogen phosphate dodecahydrate, disodium hydrogen phosphate heptahydrate, sodium phosphate dodecahydrate ($Na_3PO_4 \cdot 12H_2O$), dipotassium hydrogen phosphate (K_2HPO_4), potassium hydrogen phosphate trihydrate

($K_2HPO_4 \cdot 3H_2O$), potassium phosphate tribasic (K_3PO_4), diammonium hydrogen phosphate ($(NH_4)_2HPO_4$), ammonium phosphate trihydrate ($(NH_4)_3PO_4 \cdot 3H_2O$), sodium hydrogen carbonate ($NaHCO_3$), sodium carbonate Na_2CO_3, or mixtures thereof.

35. The method as claimed in any of claims 16-34, further comprising subjecting the hardened calcium phosphate article to one or more heat treatments, wherein the temperature of the heat treatments is from about 50 °C to about 500 °C.

36. A shaped porous calcium phosphate article comprising:
a substantially hardened calcium phosphate cement body;
wherein the article is shaped for use as a medical implant, and wherein the porosity of the article is about 20% to about 90%, wherein the porous calcium phosphate article has a compressive strength that is greater than about 0.4 MPa.

37. A shaped porous calcium phosphate article comprising:
a substantially hardened calcium phosphate cement body;
wherein the article is shaped for use as a medical implant, wherein the porosity of the article is about 20% to about 90%, wherein at least a portion of the calcium phosphate cement is substantially particulate, and wherein at least a portion of the particles comprising the calcium phosphate cement comprise whiskers on the surface thereof.

38. The shaped porous calcium phosphate article as claimed in claims 36 or 37, wherein the hardened calcium phosphate cement body is made from at least one calcium phosphate source.

39. The shaped porous calcium phosphate article as claimed in claim 38, wherein the calcium phosphate source comprises alpha-tricalcium phosphate (α-TCP), beta- tricalcium phosphate (β-TCP), tetracalcium phosphate (TTCP), monocalcium phosphate monohydrate (MCPN), monocalcium phosphate anhydrous (MCPA), dicalcium phosphate dihydrate (DCPD), dicalcium phosphate anhydrous (DCPA), octacalcium phosphate (OCP), calcium dihydrogen phosphate, calcium dihydrogen phosphate hydrate, acid calcium pyrophosphate, anhydrous calcium hydrogen phosphate, calcium hydrogen phosphate hydrate, calcium pyrophosphate, calcium triphosphate, calcium phosphate tribasic, calcium polyphosphate, calcium metaphosphate, anhydrous tricalcium phosphate, tricalcium phosphate hydrate, amorphous calcium phosphate, or mixtures thereof.

40. The shaped porous calcium phosphate article as claimed in claim 38, wherein at least a portion of the calcium phosphate cement is made from tetracalcium phosphate.

41. The shaped porous calcium phosphate article as claimed in claim 38, wherein at least a portion of the calcium phosphate cement is made from tetracalcium phosphate and dicalcium phosphate anhydrous.

42. The shaped porous calcium phosphate article as claimed in claim 38, wherein at least a portion of the calcium phosphate cement made from apatite.

43. The shaped porous calcium phosphate article as claimed in claim 42, wherein the molar ratio of calcium/phosphate of the apatite is about 1.5 – 2.0.

44. The shaped porous calcium phosphate article as claimed in claim 38, wherein at least a portion of the calcium phosphate cement is made from tetracalcium phosphate particles, and wherein at least a portion of the tetracalcium phosphate particles comprise whiskers on the surface of the particles.

45. A method of forming a porous calcium phosphate article comprising:
adding a porous component paste to a mold, wherein the porous component paste comprises at least one calcium phosphate cement combined with at least one pore forming agent and at least one setting agent;
forming a hardened calcium phosphate article form the porous component paste; and
immersing the hardened calcium phosphate article in one or more immersing liquids to form the porous article.

46. The method as claimed in claim 45, wherein immersing the hardened calcium phosphate article in one or more immersing liquid comprises:

immersing the hardened calcium phosphate article in a first immersing fluid for a predetermined time, wherein immersing the hardened calcium phosphate article in the first immersing fluid removes at least a portion of the pore forming agent from the hardened calcium phosphate article; and

immersing the hardened calcium phosphate article in a second immersing fluid for a predetermined time, wherein immersing the hardened calcium phosphate article in the second immersing fluid increases the compressive strength of the resulting porous article.

47. The method as claimed in any of claims 45 or 46, wherein immersion of the hardened calcium phosphate article is carried out at a temperature of from about 10 °C to about 90 °C.

48. The method as claimed in any of claims 45-47, wherein the hardened calcium phosphate article is immersed in at least one immersing liquid for a time period sufficient to remove at least a portion of the pore forming agent from one or more porous components.

49. The method as claimed in any of claims 45-48, wherein the hardened calcium phosphate article is immersed in at least one immersing liquid for at least 10 minutes or for at least 24 hours.

50. The method as claimed in any of claims 45-49, wherein at least one immersing liquid comprises at least one source of calcium and at least one source of phosphate.

51. The method as claimed in any of claims 45-49, wherein at least one immersing liquid comprises Hank's solution.

52. The method as claimed in any of claims 45-49, wherein at least one immersing liquid comprises substantially pure water.

53. The method as claimed in any of claims 45-52, wherein the pore-forming agent comprises an inorganic salt.

54. The method as claimed in any of claims 45-52, wherein the pore-forming agent comprises an organic salt.

55. The method as claimed in any of claims 45-53, wherein the porous component paste comprises at least one calcium phosphate source, and the load bearing component paste comprises at least one calcium phosphate source.

56. The method as claimed in claim 55, wherein the calcium phosphate source comprises alpha-tricalcium phosphate (α-TCP), beta-tricalcium phosphate (β-TCP), tetracalcium phosphate (TTCP), monocalcium phosphate monohydrate (MCPM), monocalcium phosphate anhydrous (MCPA), dicalcium phosphate dihydrate (DCPD), dicalcium phosphate anhydrous (DCPA), octacalcium phosphate (OCP), calcium dihydrogen phosphate, calcium dihydrogen phosphate hydrate, acid calcium pyrophosphate, anhydrous calcium hydrogen phosphate, calcium hydrogen phosphate hydrate, calcium pyrophosphate, calcium triphosphate, calcium phosphate tribasic, calcium polyphosphate, calcium metaphosphate, anhydrous tricalcium phosphate, tricalcium phosphate hydrate, or mixtures thereof.

57. The method as claimed in claim 55, wherein the calcium phosphate source comprises tetracalcium phosphate, wherein at least a portion of tetracalcium phosphate particles comprises whiskers on the surface of the tetracalcium phosphate particles.

58. The method as claimed in any of claims 45-57, wherein at least one of the setting agents comprises substantially pure water.

59. The method as claimed in any of claims 45-57, wherein at least one of the setting agents comprises an acidic solution, and wherein the acidic solution comprises nitric acid (HNO_3), hydrochloric acid (HCl), phosphoric acid (H_3PO_4), carbonic acid (H_2CO_3), sodium dihydrogen phosphate (NaH_2PO_4), sodium dihydrogen phosphate monohydrate ($NaH_2PO_4 \cdot H_2O$), sodium dihydrogen phosphate dihydrate, sodium dihydrogen phosphate dehydrate, potassium dihydrogen phosphate (KH_2PO_4), ammonium dihydrogen.phosphate ($NH_4H_2PO_4$), malic acid, acetic acid, lactic acid, citric acid, malonic acid, succinic acid, glutaric acid, tartaric acid, oxalic acid or mixtures thereof.

60. The method as claimed in any of claims 45-57, wherein at least one of the setting agents comprises a basic solution, and wherein the basic solution comprises ammonia, ammonium hydroxide, alkali metal hydroxide, alkali earth hydroxide, disodium hydrogen phosphate (Na_2HPO_4), disodium hydrogen phosphate dodecahydrate, disodium hydrogen phosphate heptahydrate, sodium phosphate dodecahydrate ($Na_3PO_4 \cdot 12H_2O$), dipotassium hydrogen phosphate (K_2HPO_4), potassium hydrogen phosphate trihydrate ($K_2HPO_4 \cdot 3H_2O$), potassium phosphate tribasic (K_3PO_4), diammonium hydrogen phosphate ($(NH_4)_2HPO_4$), ammonium phosphate trihydrate ($(NH_4)_3PO_4 \cdot 3H_2O$), sodium hydrogen carbonate ($NaHCO_3$), sodium carbonate Na_2CO_3, or mixtures thereof.

61. The method of as claimed in any of claims 45-60, further comprising subjecting the porous component paste to a pressure of greater than about 1 MPa or between about 1 MPa to about 500 MPa to form the hardened calcium phosphate article.

62. The method as claimed in any of claims 45-61, further comprising subjecting the hardened calcium phosphate article to one or more heat treatments, wherein the temperature of the heat treatments is from about 50 °C to about 500 °C.

63. A method of forming a molded calcium phosphate article comprising:

adding a paste comprising at least one calcium phosphate cement and at least one setting agent to a mold, wherein the setting agent comprises a liquid;

displacing at least a portion of the liquid from the paste to form a hardened calcium phosphate article; and

immersing the hardened calcium phosphate article in at least one impregnating fluid to form the molded calcium phosphate article.

64. A method of forming a molded calcium phosphate article comprising:

adding a paste comprising at least one calcium phosphate cement and at least one setting agent to a mold;

subjecting the paste to a molding pressure or greater than about 1 MPa to form a hardened calcium phosphate article; and

immersing the hardened calcium phosphate article in at least one impregnating fluid to form the molded calcium phosphate article.

65. The method as claimed in any of claims 63 or 64, wherein the impregnating liquid is an acidic solution, a basic solution, a physiological solution, an organic solvent, or a substantially pure water.

66. The method as claimed in any of claims 63 or 64, wherein the impregnating liquid comprises at least one of Ca and P sources.

67. The method as claimed in any of claims 63 or 64, wherein the impregnating liquid is a Hanks' solution.

68. The method as claimed in any of claims 63-67, wherein the impregnating is carried out for a period longer than 10 minutes or between about 12 hours to about 96 hours.

69. The method as claimed in any of claims 63-68, wherein the impregnating is carried out at room temperature or at a temperature between about 30 and 90°C.

70. The method as claimed in any of claims 63-69, wherein said calcium phosphate cement comprises one or more calcium phosphates selected from the group consisting of alpha-tricalcium phosphate (α-TCP), beta-tricalcium phosphate (β-TCP), tetracalcium phosphate (TTCP), monocalcium phosphate monohydrate (MCPM), monocalcium phosphate anhydrous (MCPA), dicalcium phosphate dihydrate (DCPD), dicalcium phosphate anhydrous (DCPA), octacalcium phosphate (OCP), calcium dihydrogen phosphate, calcium dihydrogen phosphate hydrate, acid calcium pyrophosphate, anhydrous calcium hydrogen phosphate, calcium hydrogen phosphate hydrate, calcium pyrophosphate, calcium triphosphate, calcium phosphate tribasic, calcium polyphosphate, calcium metaphosphate, anhydrous tricalcium phosphate, tricalcium phosphate hydrate, and amorphous calcium phosphate.

71. The method as claimed in any of claims 63-69, wherein the calcium phosphate source cement at least one calcium phosphate particle having calcium phosphate whiskers on the surface of said calcium phosphate particle, wherein said calcium phosphate whiskers have a length of about 1-5000 nm and a width of about 1-500 nm.

72. The method as claimed in any of claims 63-71, further comprising heating the paste during molding.

73. The method as claimed in any of claims 63-72, further comprising heating the impregnating liquid during impregnating.

74. The method as claimed in any of claims 63-73, further comprising heating the molded calcium phosphate article after removing the article from said impregnating liquid.

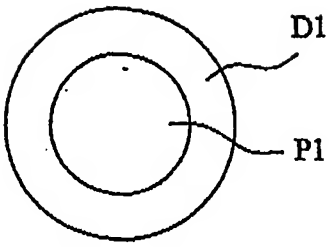

FIG. 1a

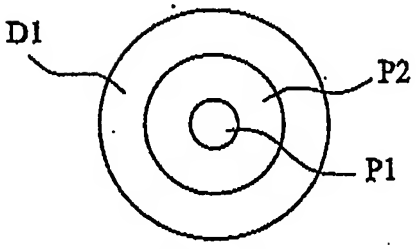

FIG. 1b

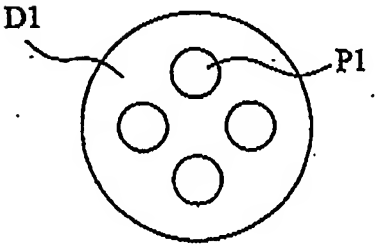

FIG. 1c

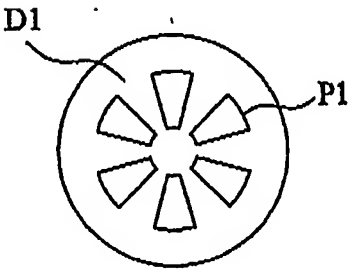

FIG. 1d

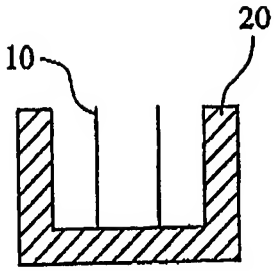

FIG. 2a

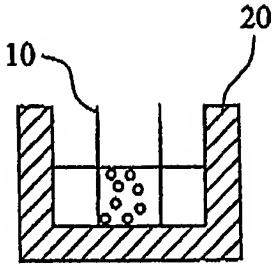

FIG. 2b

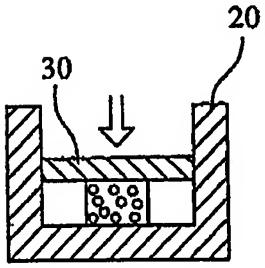

FIG. 2c

FIG. 2d

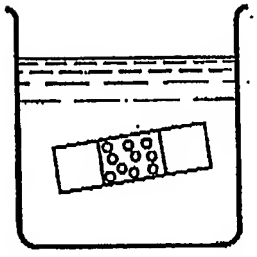

FIG. 2e

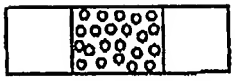

FIG. 2f

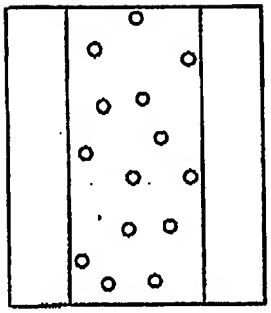

FIG. 3a

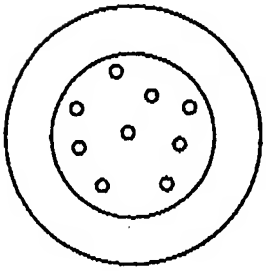

FIG. 3b

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/006100

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L27/12 A61L27/56 A61F2/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2005/016616 A (LIN, JIIN-HUEY, CHERN; JU, CHIEN-PING) 24 February 2005 (2005-02-24) page 5, line 9 - page 6, line 22 page 8, line 5 - page 9, line 20	36-74
X	US 6 149 688 A (BROSNAHAN ET AL) 21 November 2000 (2000-11-21) column 2, line 44 - line 65 column 4, line 11 - line 41; claims 1,3	1-15,36
X	US 2003/167093 A1 (XU HUAKUN ET AL) 4 September 2003 (2003-09-04)	36,45-62
Y	column 5, paragraphs 34,35; examples 1,13,16	37-44

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
28 June 2005	05/07/2005

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/006100

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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